REMARKS

Claims 1, 7, 8 and 26-28 are pending in the application. Each of the claims has been rejected.

Upon entry of the amendment to the claims, claims 26-28 will be canceled and claims 1, 7 and 8 will be pending.

No new matter has been added. Entry of the amendment is respectfully requested.

I. Rejection Under 35 U.S.C. §103

At page 2 of the office action, the rejection of claims 1, 7, 8 as being unpatentable under 35 U.S.C. §103(a) over Elgersma (2002), Wang (2003), Hanson (1994) and Sutoo (2002) has been maintained and extended to claims 26-28.

As a basis for the rejection, the Examiner stated in the office action dated July 9, 2009, that the "claimed knock-in animals are essentially disclosed by Wang et al with the exception of the phenotype limitation in claim 2" (page 5, office action dated July 9, 2009), that the use of the mutant of Hanson with the knock-in animals of Wang or Elgersma would have been obvious, and that the skilled artisan would have been motivated to produce the claimed knock-in animals to further knowledge on the role of CaMKIIα in memory and learning. The Examiner concludes that "the totality of the prior art teaches the predictable generation of CaMKIIα mutants with the claimed activity."

Applicants respectfully traverse the Examiner's position for the reasons of record and for the following additional reasons.

In particular, Applicants re-assert their position that the combined disclosure provided by the cited documents would not have yielded predictable results to the skilled artisan, both for the reasons set forth in the Amendment filed August 13, 2010, and the additional reasons provided below. As stated by the U.S. Supreme Court in the seminal KSR decision, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 US 398, 416, 82 USPQ2d 1385, 1396 (2007). Applicants respectfully assert that the invention as recited in the pending claims would not have been predictable to one of ordinary skill in the art at the time of the invention.

In support of this position, Applicants reiterate in the following paragraphs the arguments set forth in the Amendment filed August 13, 2010, but include additional comments that are responsive to observations made by the Examiner.

Applicants note that in higher eukaryotes, the gene control region, which includes the promoter and all of the regulatory sequences of a gene, varies widely among genes, both in composition and location. It is well-understood that "it is not unusual to find the regulatory sequences of a gene dotted over distances as great as 50,000 nucleotide pairs" (Molecular Biology of The Cell, 4th edition, B. Alberts ed., p. 400 (2002), previously provided) and sometimes the elements of one control region overlap with those of another. It is not unusual for part of the control region of one gene to be located within introns or exons of other genes, and the exact range and entire structure of many genes remain to be determined. Thus, genetic engineering to generate a knockin mouse, even where the manipulation of an exon of the target gene is limited and the exogenous DNA segment introduced into an intron is small, could easily result in disruption of the gene control region of the target gene or another, non-target gene that is important for early development, survival or breeding. Therefore, one skilled in the art would readily recognize that a combination of art disclosing a particular gene and means for disrupting that gene does not unerringly lead to successful generation of a knockin mouse that is viable, healthy and has reasonable reproductive power. Indeed, the skilled artisan would find it quite unpredictable as to whether such mice could be successfully produced.

In addition, successful generation of CaMKIIα knockout mice and knockin mice with Thr-305/Thr-306 modifications within the regulatory domain by Elgersma could not have served as a basis from which to predict whether the knockin mice of the present invention, having a Lys-42 modification within the catalytic domain, could be successfully generated. This is because (1) the exons and introns of the CaMKIIα gene, which consists of 18 exons and comprises more than 50,000 nucleotide pairs[1], targeted by the three groups are completely different, and (2) the cited art provides no information whatsoever as to whether the target site in the mice of the present invention is localized within part of a gene control region. As explained above, disruption of a gene control region in a gene could have a

[1] See abstract of Nishioka et al., *FEBS Letters* 396:333-336 (1996).

devastating effect on early development, survival or breeding, not to mention neonatal development and viable birth. Therefore, the combination of cited art, even with the additional knowledge from Hanson and Sutoo, cannot be said to be predictive in any way of the successful generation of the inactive CaMKIIα knockin nonhuman animal of the present invention, which has a satisfactory birthrate, survival rate, and reproduction power as described in Example 6 of the specification.

In response to these arguments, the Examiner stated in the Office Action dated March 29, 2011 (p. 3-4) that "Applicants provide a reference (Kirkwood et al) wherein CaMKIIalpha -/- mice are prepared, and such mice are viable. How then could preparing mice that actually express the CaMKIIalpha protein, albeit harboring a substitution mutation, be unpredictable or difficult when mice that COMPLETELY LACK the protein can be prepared?" In this regard, reference is respectfully made to Silva et al[2], a copy of which is submitted herewith. Silva et al describes the preparation of CaMKIIα knock-out mice (CaMKIIα mutant mice) at page 201, right column, as follows:

> **α-CaMKII mutant mice.** In order to produce mice with a mutation in the α-CaMKII locus, we constructed the plasmid p23 (Fig. 1A) which contains a 6.1 kilobase (kb) mouse genomic α-CaMKII sequence that is disrupted by insertion of a neomycin-resistance gene (*neo*) from the plasmid *pgkneo* (11). The insertion is within the α-CaMKII exon encoding most of the regulatory domain, and the inserted sequence replaced a 130-bp mouse genomic sequence flanked by a pair of Sph I sites; the expression product of the 130-bp sequence includes the entire inhibitory domain and five amino acids in the amino end of the calmodulin-binding domain (12).

As stated in Silva et al, the entire inhibitory domain and five amino acids in the amino end of the calmodulin-binding domain are substituted by a neomycin-resistance gene (*neo*) in CaMKIIα knock-out mice (KO mice). Nishioka et al shows that the "inhibitory domain" and the "calmodulin-binding domain" are encoded by exon 11 and exon 12 of CaMKIIα gene, respectively (*See* Fig. 2; lines 17-20 in the right column of page 335).[3]

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[2] Deficient Hippocampal Long-Term Potentiation in α-Calcium-Calmodulin Kinase II Mutant Mice, *Science* 257(5067):201-206 (1992).

[3] It may be helpful to note that the "autophosphorylation site" described in lines 17-19 is within the "inhibitory domain."

In contrast, CaMKIIα knock-in mice (KI mice) of the present invention are mutated in exon 2 and downstream intron 2 of the CaMKIIα gene as explained in Example 1. That is, while mutation of the CaMKIIα gene in KO mice affects a region comprising exons 11 and 12, and intron 11 in between, mutation of the CaMKIIα gene in the KI mice of the present invention affects exon 2 and intron 2. Exon 2 is located at quite a distance from exons 11 and 12 (approximately 20 kb; see Fig. 2 of Nishioka et al). Because the two genetic modifications are completely different in form and location, Applicants respectfully assert that the successful production of the KI mice of the present invention would not have been predictable, even if KO mice were successfully prepared. One of ordinary skill in the art could not have predicted whether any important control region of the CaMKIIα gene may have existed in and around exon 2, which are target sites of the present invention. Similarly, the skilled artisan could not have predicted whether this region contain regulatory elements of a non-target gene.

As a final comment, Applicants also note that the generation of knock*out* mice is generally more predictable because one seeks to simply inactivate the target protein. This can generally be accomplished by simply deleting or interrupting one or more exons, where the greater the disruption, the more likely one is to inactivate the target protein. In contrast, the successful production of knock*in* mice is much more difficult and requires greater finesse because one seeks to maintain or only alter the activity of the target protein. One cannot simply make wholesale exon deletions, and the skilled artisan would readily understand that the alteration of even one amino acid can have unpredictable effects on the activity of the protein. Therefore, the successful production of knockin mice is a much more unpredictable venture.

In view of these comments, Applicants respectfully request reconsideration and withdrawal of the rejection.

II. Double Patenting

At page 4 of the office action, claims 26-28 are objected to under 37 C.F.R. §1.75 as being substantial duplicates of claims 1, 7 and 8.

The Examiner states that claims 26-28 recite a nonhuman animal having the same genotype, but different phenotype, from the nonhuman animal of claims 1, 7 and 8. The

Examiner finds the phenotype recited in claims 26-28 to be "nothing more than a general assay for neuronal activity" and therefore the scope of these two groups of claims does not differ.

In response, Applicants note that claims 26-28 are being canceled, thus making this objection moot. In view thereof, reconsideration and withdrawal of the objection is respectfully requested.

III. Conclusion

In view of the above amendments and remarks, Applicants respectfully request a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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